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Alveolar Hydatid Disease in Minnesota: First Human Case Acquired in the Contiguous United States

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Alveolar Hydatid Disease in Minnesota

First Human Case Acquired in the Contiguous United States

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• **A 56-year-old woman from southwestern Minnesota underwent an extended left hepatic lobectomy to remove a large multinodular mass with a necrotic central cavity. The clinical, serological, and pathological findings led to the diagnosis of alveolar hydatid disease, and specific identification of *Echinococcus multilocularis* was achieved by growing mature larvas in voles inoculated intraperitoneally with tissue from the hepatic lesions. The patient probably acquired her infection some years previously from pet cats or dogs that had become infected by ingesting infected rodents. In North America *E multilocularis* is enzootic in the northern tundra zone of Alaska and Canada. Since 1964 the cestode has been recognized with increasing frequency in several north-central states, including Minnesota. The parasite may extend its range farther south, since suitable animal hosts occur throughout the United States.**

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ALVEOLAR hydatid disease is an infection caused by the larval stage of the zoonotic parasite *Echinococcus multilocularis* Leuckart, 1863. The natural intermediate hosts of this cestode are small rodents. The natural definitive hosts for the tapeworm stage are foxes. Domestic dogs and cats are also susceptible definitive hosts and may become part of the life cycle when they prey on infected wild rodents. Although infections in carnivores are usually asymptomatic, their feces contain the eggs of the tapeworm, which are infective if accidentally ingested by susceptible intermediate hosts, including humans. In man the insidious, progressive growth of the hepatic larval lesion makes alveolar hydatid disease one of the most lethal of parasitic diseases. By the time the disease is clinically manifest, the lesion is often inoperable, and case-fatality ratios range from 50% to 70%.[1]

In North America *E multilocularis* is enzootic in the northern tundra zone in cycles involving arctic foxes and their rodent prey.[1] Since 1964 the cestode has been recognized with increasing frequency in animal hosts from several north-central states, including Minnesota; however, to our knowledge, infections in man had not been previously recognized in the contiguous United States.

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REPORT OF A CASE

A 56-year-old woman was admitted to a local hospital in southwestern Minnesota on July 15, 1977, complaining of epigastric discomfort and malaise of several weeks' duration. Jaundice, dark urine, and acholic stools were noted three days before admission.

Examination showed epigastric fullness and the suggestion of a palpable mass. The alkaline phosphatase value was 556 IU, the bilirubin value was 13.4 mg/dL, and the SGOT value was 48 units. The upper gastrointestinal (GI) series was normal.

Exploratory laparotomy was performed, and the surgeon reported metastatic carcinoma involving the left lobe of the liver. Further exploration of the abdomen did not show a primary site, and it was suspected that there was an occult primary carcinoma of the pancreas. The pathologist's report subsequently indicated cholestasia with periportal chronic inflammation and large zones of liver cell necrosis and hyalinization.

On July 25, 1977, the patient was transferred to a hospital in Minneapolis for further evaluation. Repeated serum chemistries suggested obstructive jaundice, and because of the uncertainty of the diagnosis, reexploration was performed. A multinodular, umbilicated, cystic, pale gray mass, 12 cm in diameter, was noted replacing the medial segment of the left lobe of the liver, with nodular extension into the lateral segment and slightly across the surgical plane between the right and left lobes.

Operative cholangiography demonstrated compressive obstruction of the common hepatic and main-branch intrahepatic ducts by the large mass. A full-thickness biopsy specimen of the wall of

the mass was examined by frozen section, and the pathologist reported probable echinococcal cyst disease. The cyst was decompressed through a large-bore external drainage catheter, with release of 450 mL of slightly turbid, serosanguineous fluid. Postoperatively the patient's condition improved dramatically, with rapid clearing of the jaundice, and she was discharged one week after surgery.

The patient was readmitted to the hospital on Oct 23, 1977, for definitive resection. On Oct 26 an extended left hepatic lobectomy was performed. The patient made an uneventful recovery and was discharged on the 16th postoperative day. She was treated with mebendazole at a dosage of 40 mg/kg/day, beginning three days preoperatively and continuing for four months. When last examined 12 months after hepatic resection, the patient appeared clinically well and had regained her normal weight and level of activity. Abdominal examination showed no evidence of hepatomegaly, the sinus tract had healed, and the liver function studies have remained normal, with the exception of mild elevation of the alkaline phosphatase level (60 IU). Liver scan showed no change in comparison with the postoperative examination.

PATHOLOGICAL AND PARASITOLOGICAL FINDINGS

The lesion involved the entire left lobe and a portion of the right lobe of the liver. The larval mass measured 12-cm maximum dimension, with a necrotic central cavity of 9-cm diameter. The resected tissue weighed 335 g. On cut surface the lesion consisted of pale, dense nodules and cystic areas surrounding the central cavity and infiltrating liver tissue peripherally (Fig 1). Microscopically the lesion contained numerous microvesicles lined by a laminated hyaline membrane surrounded by a granulomatous reaction and embedded in a dense connective-tissue matrix. Inside the laminated membranes, which stained intensely with periodic acid-Schiff and Grocott methenamine silver stains, there were thin germinative layers that contained small nuclei (Fig 2). In the zones of cellular reaction, which occurred perifocally around the microvesicles, histiocytes preponderated, but lymphocytes, plasma cells, and eosinophils were numerous throughout. There were some areas of degenerative changes and necrosis. There was no indication of the formation of protoscolices or of calcareous corpuscles.

A portion of the freshly resected lesion was minced finely and inoculated intraperitoneally into six red-backed voles, *Clethrionomys rutilus* (Pallas), ten meadow voles, *Microtus pennsylvanicus* (Ord), and six jirds, *Meriones unguiculatus* (Milne-Edwards). These laboratory-reared animals were killed at varying intervals between two and four months after inoculation. Viable cysts were observed in the peritoneum of two of the six red-backed voles. One lesion, examined four months after inoculation, had microscopic structure characteristic of larval *E multilocularis* as described by Rausch and Wilson.[2]

Echinococcus antibodies, determined by three serological tests, were present in the patient's serum at low levels before resection of the lesion, increased notably immediately postoperatively, and then declined slowly (Table).

EPIDEMIOLOGIC FINDINGS

The patient had lived all of her life on farms within a 32-km radius of her present residence in Lyon County, Minnesota. She had traveled out of the state on separate occasions to Hawaii (1975), Florida (1974), California (1968, 1973, 1976), and Winnipeg, Manitoba (1963, 1970). The trips to Winnipeg involved overnight stays during which the patient recalled no contact with dogs, cats, or other animals.

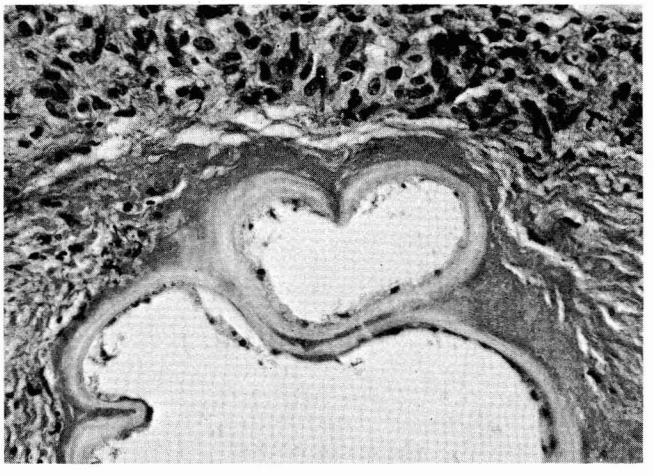
The patient and her family had resided at the present farm for 22 years. The main products of the farm

	Echinococcus Antibodies*		
Date	Indirect Hemagglutination	Bentonite Flocculation	Immunoelectrophoresis, Bands
8/2/77	1:256	1:10	0
11/13/77	1:2,048	1:160	2†
3/27/78	1:128	1:20	2‡

*Tests performed in parallel on all serum specimens at the Center for Disease Control, Atlanta.
†Included *Echinococcus*-specific arc 5.
‡Weak bands, unidentified.

Fig 1.—Cut surface of resected liver specimen. Necrotic central cavity (lower portion) surrounded by pale, infiltrating granulomatous zone.

Fig 2.—Magnification of specimen. Thin germinative layers are seen inside laminated membranes (hematoxylin-eosin, ×300).



are soybeans and corn. A few cattle and sheep are kept but are never butchered on the premises. The family has always had at least one pet dog and five to ten cats. The cats and dogs do not enter the house, but the patient handled them occasionally while doing chores in the barn. The family has had the current pet dog for 1½ years, and stool specimens obtained from this dog and examined by the formalin-ether concentration technique on three consecutive days were negative for taeniid ova. Six house mice, *Mus musculus* (Linnaeus); and one deer mouse, *Peromyscus maniculatus* (Wagner), were trapped on the farm and were negative for infection by the larval cestode at necropsy.

Serum specimens collected from the patient's husband, son, daughter-in-law, and granddaughter, who live on a neighboring farm, were nonreactive in serological tests for echinococcosis.

COMMENT

The clinical, serological, and pathological findings in this case led to the diagnosis of alveolar hydatid disease. The specific identification of *E multilocularis* was achieved by recovery of mature larvas from laboratory-raised voles that had been inoculated intraperitoneally with suspensions of larval tissues from the hepatic lesion removed at surgery. The patient had not traveled to areas where human alveolar hydatid disease has been reported to occur; thus, to our knowledge, this is the first locally acquired case of *E multilocularis* infection diagnosed within the contiguous 48 states. To our knowledge there are no previous reports from this geographic region, with the exception of three cases diagnosed in persons who had recently emigrated from other endemic areas where they had most likely acquired their infections.[3-5]

The primary localization of *E multilocularis* larvas in human beings, as well as in natural intermediate hosts, is the liver. The larval mass proliferates indefinitely by exogenous budding, progressively invading the surrounding tissues, and resembles a malignant neoplasm in behavior and appearance. There may be metastases to the lungs or brain. In chronic infections the lesion consists of a central necrotic cavity filled by a white amorphous material and a thin peripheral layer of dense fibrous tissue that is extensively infiltrated by the proliferating vesicles. Protoscolices (mature larval units) are rarely observed in infections in man, and the histopathologic findings may be confusing; eosinophilic laminated hyaline material, necrotic liver tissue, and fibrous tissue are found in patternless disorder. It had been shown previously, however, that under conditions of an adverse parasite-host relationship, undifferentiated larval cells retain their generative potential, and when tissues containing such cells are transferred to a favorable host environment, histogenesis can occur normally.[2] This characteristic was exploited in our case to permit confirmation of the causative agent as *E multilocularis*.

The long-term prognosis for our patient is relatively favorable because most, if not all, of the larval cestode lesion was removed at surgery. To minimize chances for recurrence of larval growth, the patient was given oral mebendazole, which destroys larval cestodes in experimental animals and, in preliminary studies, appears to cause regression of hydatid cysts of *E granulosus*[6] and *E multilocularis*[7] in human patients.

Echinococcus multilocularis was first recognized in North America in the early 1950s, and since then 32 cases of human alveolar hydatid disease have been diagnosed in the northern tundra zone of Alaska. Since 1964 the cestode has been identified in animal hosts from an increasingly large area of central North America, including North Dakota,[8-10] South Dakota,[9] Minnesota,[11] Iowa,[9] Montana,[9,12] Wyoming,[13] Manitoba,[14-16] Saskatchewan,[17-19] and Alberta.[20] The important sylvatic hosts in these regions are red foxes, coyotes, deer mice, and field voles. The importation of the cestode into the central North American focus may have occurred by transport of infected dogs from Alaska[21] or by southward migration of infected arctic foxes. The diagnosis of a human case of hydatid disease in Manitoba in 1928,[22] which, in retrospect, was apparently a locally acquired case of *E multilocularis*, suggests that the cestode has been present there at least since the 1920s.

In Minnesota extensive parasitological surveys of foxes and rodents documented the absence of *E multilocularis* through the 1940s.[23-25] The cestode was first recognized in Minnesota as a result of studies carried out between 1965 and 1968 when infection was found in 5% of 277 foxes captured in various localities in the state.[11] Since then the cestode has greatly increased its range and prevalence rate. A conversation with F. J. Vande Vusse, PhD (Nov 9, 1978) disclosed that a survey of foxes carried out in the winter of 1977 to 1978 has shown infection in 49% of more than 250 foxes, thereby extending the known range of *E multilocularis* from four to 20 counties in southwestern Minnesota.

Recent infections in pets or wild animals would not be the source of infection for this patient because more than ten years may elapse before clinical signs of disease in humans become apparent, but infections in carnivores are self-limiting after several months.[26] Therefore, we can only guess at the particular source of infection in this case. Neither the patient nor her family engaged in hunting or other activities likely to expose her to foxes. It is more likely that the infection was acquired from a cat or dog that had eaten an infected vole or deer mouse. Although these pets did not enter the patient's house, their feces containing cestode eggs may have been carried into the house on contaminated clothing or footwear, or the patient might have been exposed while working outside. According to written communications from Delane C. Kritsky, PhD, and Paul Leiby, PhD (May 16, 1978), infection in cats is a distinct possibility because recent surveys of farm cats in North Dakota have shown infection rates varying from 1% to 5% during the years 1971 to 1976.

The introduction and spread of *E multilocularis* into Minnesota and adjacent states has serious implications. When restricted to sylvatic hosts, human exposure would be relatively uncommon except for hunters and other persons who might handle foxes or their skins. However, the enzootic occurrence of the cestode in local rodents represents a constant potential source of infection for cats

and dogs in rural areas, and effective prevention could only be achieved by maintaining absolute control of movement of such pets at all times—a measure that is impractical.

Suitable sylvan animal hosts are present throughout most of the United States, and there are few barriers to prevent further extension of the cestode southward and eastward. If the parasite becomes established in cycles involving cats and house mice, it would permit entry into urban areas and even greater potential exposure of humans.[27] More optimistically the apparent potential for widespread human infection may be limited by the low susceptibility of the human as host, as evidenced by the relatively low incidence of disease in some heavily exposed Alaskan Eskimo populations.

Ortho Pharmaceutical Co, Raritan, NJ, provided mebendazole.

Nonproprietary Name and Trademark of Drug

Mebendazole—*Vermox.*

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